Personalized Medicine in Diabetes

Noemi Malandrino and Robert J. Smith*

BACKGROUND: Multiple genes that are associated with the risk of developing diabetes or the risk of diabetes complications have been identified by candidate gene analysis and genome-wide scanning. These molecular markers, together with clinical data and findings from proteomics, metabolomics, pharmacogenetics, and other methods, lead to a consideration of the extent to which personalized approaches can be applied to the treatment of diabetes mellitus.

CONTENT: Known genes that cause monogenic subtypes of diabetes are reviewed, and several examples are discussed in which the genotype of an individual with diabetes can direct considerations of preferred choices for glycemic therapy. The extent of characterization of polygenic determinants of type 1 and type 2 diabetes is summarized, and the potential for using this information in personalized management of glycemia and complications in diabetes is discussed. The application and current limitations of proteomic and metabolomic methods in elucidating diabetes heterogeneity is reviewed.

SUMMARY: There is established heterogeneity in the determinants of diabetes and the risk of diabetes complications. Understanding the basis of this heterogeneity provides an opportunity for personalizing prevention and treatment strategies according to individual patient clinical and molecular characteristics. There is evidence-based support for benefits from a personalized approach to diabetes care in patients with certain monogenic forms of diabetes. It is anticipated that strategies for individualized treatment decisions in the more common forms of diabetes will emerge with expanding knowledge of polygenic factors and other molecular determinants of disease.

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Personalized medicine in diabetes refers to the use of specific characteristics of a patient to direct diagnostic or treatment strategies that are most effective for that individual. The spectrum of information that can guide personalized decisions on diabetes care includes individual behavioral and clinical phenotypic features, standard clinical laboratory findings, and gene sequences and other molecular markers. Given the remarkable progress over the past few years in characterization of human gene sequences and in additional new molecular technologies, there is particular interest in the potential for using individual molecular biomarkers to direct patient-specific decisions on the management of diabetes. Technological advances in genetics, genomics, proteomics, and metabolomics make possible the efficient analysis of thousands of genes, proteins, and metabolites, thus offering new opportunities for identifying genetic factors and gene products that are linked to different subtypes of diseases such as diabetes mellitus (1). In addition to improving clinical outcomes, it is anticipated that greater knowledge of genetic and protein factors will provide novel mechanistic insights into the pathogenesis of diabetes and refine predictions of disease risk, development, progression, and clinical course. Furthermore, pharmacogenetics and pharmacogenomics, which involve gene-focused and larger-scale genome-wide analyses, respectively, can specifically provide new information on genetic variations affecting efficacy and individualized susceptibility to side effects of drugs (2, 3).

Diabetes mellitus has long been recognized to be a complex, heterogeneous disorder, and it thus represents a human disease poised for substantial benefit from personalized approaches to treatment. Especially in patients fitting the broad category of type 2 diabetes, there is substantial variability in genetic risk factors, underlying pathogenic mechanisms, and clinical features. Nevertheless, patients with type 2 diabetes often are treated similarly, with little consideration of individual characteristics that might affect clinical outcome and therapeutic response (4). This review will examine current knowledge of heterogeneity in diabetes and consider the actuality and potential of personalized medicine in diabetes management.

Heterogeneity of Diabetes Mellitus

Diabetes mellitus is not a single disease, but a group of metabolic disorders with the common feature of in-
creased blood glucose concentrations in the fasted and/or fed state (5). Increased glucose concentrations may be related to absolute or relative deficits in insulin secretion, defects in insulin action, or both of these abnormalities in combination. Different pathogenic mechanisms are involved in the development of various forms of diabetes, including genetic and environmentally determined alterations in the action of insulin, the development and survival of islet β-cells, and the secretion of insulin (5). Within this spectrum of diabetes pathophysiology and subtypes, there are established differences in approaches to treatment. For example, patients with type 1 diabetes, whether diagnosed by clinical features or the presence of typical autoantibodies, are expected to require early insulin treatment as a consequence of their extensive loss of insulin secretory capacity. By contrast, patients with type 2 diabetes often can be managed effectively with lifestyle modifications and/or oral hypoglycemic agents that are effective because there is substantial residual insulin secretion. For the subgroup of type 2 diabetes patients who have morbid obesity, bariatric surgery is recognized as a specific therapeutic option that can be strikingly effective (6). Multiple studies have shown that approximately 80% of appropriately selected obese patients with established diabetes will have enough improvement of blood glucose concentrations after bariatric surgery to enable discontinuation of all glucose-lowering medications (7–12). Although the long-term course and consequences of gastric reduction and intestinal bypass surgery require further study, consideration of bariatric surgery is now broadly recommended for diabetes patients with body mass index ≥ 35 kg/m² or 30–35 kg/m² in the context of poor diabetes control and diabetes complications (6). These differences in therapeutic approach to patients with type 1 and type 2 diabetes, with or without coincident morbid obesity, represent a step towards personalized medicine. However, patients within each of these broad categories of diabetes have a spectrum of underlying causal etiologies and associated features that provide great potential for more individually defined personalized approaches to treatment.

**Monogenic Diabetes Subtypes**

As specific subtypes of diabetes that may appear clinically to fit into the categories of type 1 or type 2 diabetes, there now are at least 27 known subtypes of diabetes secondary to single-gene mutations (Table 1). Among these monogenic forms of diabetes, the specific genetic abnormalities determine clinical presentation and, for an expanding number of genes, should influence decisions on specific treatment options (4, 13).

This has been most clearly demonstrated for several of the genes responsible for the syndrome designated maturity-onset diabetes of the young (MODY) (1, 13). MODY 2 patients have mutations in the glucokinase (hexokinase 4) (GCK) gene, which decrease the affinity of this enzyme for glucose and thus shift glucose-regulated insulin secretion to a higher-than-normal glucose concentration. Affected individuals have insulin secretion that is tightly coupled with blood glucose, but they regulate to higher-than-normal concentrations. This scenario results in modestly increased blood glucose in the fasted and postprandial states such that hemoglobin A₁c values are typically in the range of 6% to 7%. Treatment with oral hypoglycemic agents or insulin in most MODY 2 patients appears to result in little improvement in blood glucose control, and the degree of increase in average blood glucose is small enough that, even in untreated patients, there may be little or no increase in long-term complications of diabetes. A recent report showed that these patients, once correctly diagnosed, often can be successfully transferred off all treatment (13). It therefore is suggested that MODY 2 patients be evaluated for management off all hypoglycemic agents except during pregnancy.
<table>
<thead>
<tr>
<th>Disease region/gene</th>
<th>Chromosome</th>
<th>Protein/gene function</th>
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<td>β-Cell K&lt;sub&gt;ATP&lt;/sub&gt; channel modulator, sulfonylurea response</td>
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<tr>
<td>INSR</td>
<td>19p13.3-p13.2</td>
<td>Insulin signaling</td>
</tr>
</tbody>
</table>

From Smith et al. (4).

* Human genes: PDX1, pancreatic and duodenal homeobox 1; HNF1B, HNF1 homeobox B; NeuroD1, neurogenic differentiation 1; IDDM2, insulin-dependent diabetes mellitus 2; PTF1A, pancreas specific transcription factor, 1a; FOXP2, forkhead box P3; EII2AK3, eukaryotic translation initiation factor 2-beta kinase 3; WFS1, Wolfram syndrome 1 (wolframin); CISD2, CDGSH iron sulfur domain 2; WRN, Werner syndrome, RecQ helicase-like; FXN, frataxin; HFE, hemochromatosis; SLCT19A2, solute carrier family 19 (thiamine transporter), member 2; AGPAT2, 1-acylglycerol-3-phosphosphate O-acetyltransferase 2 (lysocephosphatic acid acetyltransferase, beta); BSCL2, Berardinelli-Seip congenital lipodystrophy 2 (seipin); CAV1, caveolin 1, caveola protein, 22kDa; LMNB2, lamin B2; ZMPSTE24, zinc metallopeptidase (STE24 homolog, S. cerevisiae); PPARG, peroxisome proliferator-activated receptor gamma; AKT2, v-akt murine thymoma viral oncogene homolog 2; INSR, insulin receptor.

<sup>1</sup> ER, endoplasmic reticulum stress.
when a period of insulin treatment may be needed to prevent islet hyperplasia in the non-MODY offspring of a MODY 2 mother (14).

Patients with MODY 1 and MODY 3 have mutations in 1 of 2 transcription factors: hepatocyte nuclear factor 4α (HNF4A) and hepatocyte nuclear factor 1α (HNF1A), respectively, which are thought to control the expression of genes that alter pancreatic β-cell development and survival. MODY 1 and 3 patients can have markedly increased blood glucose levels and, together with their frequent onset of diabetes under the age of 25 years, this can result in a misdiagnosis as type 1 diabetes. However, individuals with MODY 1 and 3 diabetes, in contrast to patients with type 1 diabetes, often have high sensitivity to sulfonylureas. They frequently can be effectively managed with sulfonylureas, and it may be possible to transition them from insulin to sulfonylureas with a resulting improvement in blood glucose control, even after many years of treatment with insulin (15). Additional data have shown that patients with MODY 3 are more responsive to sulfonylureas than metformin (16). Several case reports have suggested that dipeptidyl peptidase-IV inhibitors may further improve blood glucose control when used in combination with sulfonylureas in MODY 3 patients (17, 18). More studies will be required to confirm these observations and determine whether incretin analogs have similar effects.

While reliable distinction of MODY 1, 2, and 3 from other MODY subtypes or other forms of diabetes ultimately requires identification of the specific gene mutation, clinical features can be helpful in selecting patients for genetic screening (19). For example, young patients with persistent mild fasting hyperglycemia in the range of 100–150 mg/dl and only a modest increase in blood glucose during oral glucose tolerance testing should be considered for MODY 2 screening. Candidate patients for MODY 1 and 3 genetic screening include individuals with diabetes under age 25 years; responsiveness to low doses of insulin; persistent undetectable C-peptide concentrations; absence of antibodies to glutamic acid decarboxylase (GAD)-65, pancreatic islet, or insulin; and a multigenerational family history suggestive of autosomal-dominant inheritance (vertical transmission). MODY 1, 2, and 3 in aggregate account for an estimated 0.5% to 1% of diabetes in US and Western European populations and thus represent a substantial number of patients in whom a correct diagnosis of diabetes subtype can direct personalized decisions on therapy. However, it is estimated that <20% of MODY patients currently are identified (20). The diagnosis and management of MODY thus represents a potential area of personalized diabetes management that needs to be more effectively implemented.

Mutations in the potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11), gene represent another example in which the genotype directs the approach to specific diabetes treatment. The KCNJ11 gene encodes the Kir6.2 subunit of the pancreatic β-cell K\textsubscript{ATP} channel, which represents a molecular target through which sulfonylureas augment insulin secretion (21). Heterozygous KCNJ11 mutations are present in approximately half of patients who develop diabetes within the first 6 months after birth, making this a subgroup of diabetes patients who can readily be selected for genetic testing. Many of these neonatal diabetes patients previously were treated with insulin, since their early onset was considered to most probably represent type 1 diabetes. However, their blood glucose concentrations often can be managed more effectively with sulfonylureas than insulin, with a decrease in hemoglobin A\textsubscript{1c} values after transition to sulfonylureas, even after many years on insulin (22, 23).

There is less information on the use of specific therapies in other monogenic subtypes of diabetes, in part because of the limited opportunity to study multiple patients with these rare disorders. To illustrate the type of data that are available, a case report showed a marked improvement in blood glucose control on treatment with a thiazolidinedione instead of metformin in a patient with lipoatrophic diabetes secondary to a mutation in the lamin A/C (LMNA) gene (24). This result appears to make mechanistic sense as an effect of thiazolidinediones on adipocyte function via the peroxisome proliferator–activated receptor (PPAR)–γ receptor in a patient with an adipocyte defect. Although diabetes in the majority of patients is not caused by a single gene mutation, the evidence for improved efficacy of specific therapies in these monogenic disorders provides a model for personalized medicine that ultimately may be applicable to patients with more common forms of diabetes defined on the basis of single or combinatorial diabetes-linked polygenic variants.

**Personalizing Type 1 and Type 2 Diabetes**

Both type 1 and type 2 diabetes are thought to be complex diseases that develop through the interplay of numerous susceptibility and protective genes, acting in concert with negative and positive environmental factors (25). Type 1 diabetes is characterized by prominent β-cell loss, often mediated by an autoimmune process, such that essentially all patients with overt type 1 diabetes require insulin. There are multiple options for insulin replacement that include different preparations of insulin and the use of intermittent injections or infusion pumps, but there are not alternatives to insulin that provide an opportunity for individualizing
treatment. Prevention of progression to type 1 diabetes in high-risk individuals, such as individuals with positive glutamic acid decarboxylase or islet autoantibodies in the context of a family history of type 1 diabetes, is an area of active investigation that may ultimately offer opportunity for personalized treatment. Multiple genetic factors have been associated with type 1 diabetes, and these genetic markers may ultimately define individualized strategies for preventing β-cell destruction. There now are >40 genetic loci associated with type 1 diabetes identified by candidate gene approaches and genome-wide association studies (26, 27). Many of the identified genes at these loci are linked to autoimmunity, whereas others appear to be functionally related to β-cell survival (28). While knowledge of these specific genes and loci does not yet have practical application in individualizing type 1 diabetes management, it can be anticipated that such genetic markers ultimately may have utility in defining personalized approaches to both prevention and treatment of type 1 diabetes. For example, the known genes include variants of HLA class II genes, which encode highly polymorphic antigen-presenting proteins and account for almost 50% of the genetic risk of type 1 diabetes (29). In addition to the utility of these gene variants in defining overall relative risk for developing diabetes, specific HLA class II alleles and haplotypes have been associated with different patterns of clinical progression of type 1 diabetes, from fulminant to acute-onset or slowly progressive (30). It is reasonable to speculate that these type 1 diabetes subtypes, and thus their associated HLA markers, may ultimately define patients who require different intensities of immunosuppressive preventive therapy, or who may differ in their requirements for immunosuppression to protect transplanted β-cells or stem cells.

Type 2 diabetes typically is characterized by a combination of abnormalities in both insulin secretion and responsiveness, plus a more gradual and less extensive loss of β-cell secretory capacity than occurs in type 1 diabetes. For this reason, available options for glycemic management in type 2 diabetes include not only exogenous insulin, but also a spectrum of pharmacologic agents with actions that include augmentation of insulin sensitivity, stimulation of insulin secretion, and slowing of intestinal glucose absorption. Candidate gene and genome-wide association studies thus far have identified at least 23 genes with sequence variations associated with type 2 diabetes across multiple populations (Table 2) (4, 25). Many additional genes have been linked to type 2 diabetes in smaller-scale studies in single populations. The contribution to disease risk by any one of these genetic factors is small (typically <1.5-fold increased risk). However, each of these identified gene variants alone or considered in combination with other genetic variants has the potential to direct individualized decisions on type 2 diabetes therapy.

Among type 2 diabetes–associated genes, polymorphisms in the transcription factor 7-like 2 (T-cell–specific, HMG-box) (TCF7L2) gene correlate with an approximately 1.4-fold increased risk of type 2 diabetes in multiple populations (31). The function of the protein encoded by this gene, a transcription factor designated “transcription factor 7-like 2,” is still under investigation. Data from TCF7L2 knockout mice and cultured cell studies indicate a range of potential functions that include effects on glucagon-like peptide 1 (GLP1) signaling in β-cells, proliferation of β-cells, and insulin secretion. A single observational study has reported a significant association of TCF7L2 polymorphisms with sulfonylurea failure but not with metformin failure (32). As a second example in which variants of a diabetes-associated gene may be linked to the efficacy of specific drugs, a single published report has shown a significant correlation of polymorphisms of the ATP-binding cassette, subfamily C (CFTR/MPR), member 8 (ABCC8), gene with sulfonylurea responsiveness in type 2 diabetes (33). Other mutations in the ABCC8 gene, which encodes the Sur1 sulfonylurea receptor in β-cells, cause neonatal diabetes, and, as noted above, these neonatal diabetes patients are often sulfonylurea sensitive. Although the differences in sulfonylurea responsiveness with both TCF7L2 and ABCC8 polymorphisms are modest and need confirmation in additional patient groups, these findings support the importance of future comparative studies on the efficacy of insulin secretagogues versus sensitizers in patients with specific type 2 diabetes–associated polymorphisms, either alone or in combination with other diabetes risk gene variants. Such studies should include an examination of patient-specific effects of pharmacologic agents on not only glycemic regulation, but also progression to type 2 diabetes.

**Personalized Pharmacology in Blood Glucose Management**

In addition to specific genetic variants that may have a causal role in diabetes, individual patient characteristics that affect responses to specific drugs have an important role in personalized diabetes management. This is a common operative in clinical practice when patients manifest intolerance of specific drugs, such as untoward side effects and allergic reactions. Rapid advances in knowledge of patient-specific pharmacology are occurring through the application of new molecular technologies in gene-focused (pharmacogenetics) and genome-wide (pharmacogenomics) analyses. Both of these approaches examine how variations in individ-
ual genetic makeup can affect the efficacy and safety profiles of drugs (34). In type 2 diabetes, polymorphisms associated with altered metformin response have been identified in the solute carrier family 22 (organic cation transporter), member 1 (SLC22A1), and solute carrier family 22 (organic cation transporter), member 2 (SLC22A2), genes (encoding the organic cation transporter 1 and 2 proteins, OCT1 and OCT2, respectively) and the solute carrier family 47, member 1 (SLC47A1), gene (encoding the multidrug and toxin extrusion 1 protein [MATE1]). These gene variants are thought to influence metformin clearance and thus the effective blood levels achieved with a given dose of metformin (35–38).

In an analogous manner, polymorphisms in the cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9), gene (encoding the P450 C29

<table>
<thead>
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<th>Region/gene</th>
<th>Chromosome</th>
<th>Approximate effect size</th>
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From Smith et al. (4) and Müller (25).

* Human genes: PPARG, peroxisome proliferator–activated receptor gamma; SLC30A8, solute carrier family 30 (zinc transporter), member 8; HHEX, hematopoietically expressed homeobox; CDKAL1, CDK5 regulatory subunit associated protein 1-like 1; CDKN2A, cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4); CDKN2B, cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4); IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; FTO, fat mass and obesity associated; HNF1B, HNF1 homeobox B; WFS1, Wolfram syndrome 1 (wolframin); JAZF1, JAZF zinc finger 1; CDC123, cell division cycle 123 homolog (S. cerevisiae); CAMK1D, calcium/calmodulin-dependent protein kinase ID; TSPAN8, tetraspanin 8; LGR5, leucine-rich repeat-containing G protein–coupled receptor 5; THADA, thyroid adenoma associated; ADAMTS9, ADAM metallopeptidase with thrombospondin type 1 motif, 9; NOTCH2, notch 2; KCNQ1, potassium voltage-gated channel, Kv7-like subfamily, member 1; MTNR1B, melanotelin receptor 1B; CAPN10, calpain 10; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1.
of only 0.48. Corresponding proteins demonstrated a correlation coefficient of 0.48. While more studies are needed, it is likely that these types of individual genetic markers ultimately will be useful in deciding the relative efficacy and dosage profiles of metformin, sulfonylureas, and other drugs in individual type 2 diabetes patients. Larger cohort studies on the known genetic variants, plus further application of genome-wide scanning methods to identify additional gene variants that influence the pharmacology of specific drugs, offer substantial potential for guiding personalized diabetes therapy.

Proteomics and Metabolomics

Genetic mutations and polymorphisms provide valid markers of disease-associated individual variability, but the changes in sequence for most genes are only indirectly related to the function of the proteins they either encode or regulate through the control of other structural genes. Changes in expression and function of proteins in an individual may be determined not only by the sequence of the gene that codes for the protein, but also by the actions of other genes and nongenetic environmental factors. This results in an imperfect correlation between genetic variation and the levels and activities of the proteins that ultimately may mediate individual disease-relevant patient characteristics. As an example, in a study that examined 19 proteins from human liver, comparison of levels of mRNA with the corresponding proteins demonstrated a correlation coefficient of only 0.48 (40). As an approach to more directly assess the abundance of proteins or their functional status (e.g., phosphorylation state), current proteomics methodology makes possible the simultaneous measurement of large numbers of proteins in the circulation, other body fluids, or tissue extracts (2, 41). The resulting data are complex, with the levels of many proteins potentially altered by a single genetic change, and proteomics data have not yet generated practical applications in personalizing approaches to diabetes management. The clinical application of proteomics approaches to individual patients is also limited by difficulties in obtaining samples of tissues of interest, such as pancreatic islets in diabetes. This is in contrast with genetic markers, which often can be determined in samples of peripheral blood or buccal mucosa, yet still provide valid insight into individual characteristics of difficult-to-access target tissues. Proteomics methodology has great potential in providing new insights into diabetes pathophysiology and identifying target proteins that may then be assessed at either the genetic or protein level, but evaluation of its application in individual patients as a guide to personalized therapy will require substantial further investigation.

Metabolomics involves the measurement of a comprehensive set of metabolites in a body fluid or tissue extract. By definition, this excludes enzymes, structural molecules, and genetic material. Metabolomics differs from proteomics in that it includes the measurement of carbohydrates, lipids, and peptides, in addition to some proteins. The goal is to define profiles of metabolites in a disease state or, potentially, in an individual that will provide insight into pathophysiology or direct specific approaches to treatment (42). The metabolome is estimated to include approximately 2500 metabolites, in contrast to the 25 000 genes and estimated 1 million different proteins that define human biology. As with proteomics, the objective of metabolomics is to gain new insight into disease pathophysiology and also identify individual metabolites or profiles of metabolites that may be useful in defining strategies for disease therapy. There are not yet established applications of this methodology in personalized diabetes management.

Personalized Medicine and Diabetes Complications

Much of the mortality of type 1 and type 2 diabetes results from long-term microvascular complications (diabetic nephropathy, retinopathy, and neuropathy) and macrovascular complications (ischemic heart disease, peripheral vascular disease, and stroke). The onset and progression of diabetes complications correlates substantially with glycemic control. Thus, each of the strategies for personalized approaches to glycemic management discussed above represents personalized management of not only blood glucose concentrations, but also diabetes complications. In addition to glycemia, the occurrence and progression of diabetes complications is strongly influenced by the presence and degree of hypertension and dyslipidemia (high LDL cholesterol, small dense LDL particles, low HDL cholesterol, and high triglycerides). Goals and strategies for lowering these nonglycemic risk factors are addressed in current medical practice guidelines (43). Just as the choice of specific drugs for management of glycemia in diabetes may be personalized, there is a similar potential for individualizing decisions on treatment and drug choice for management of nonglycemic risk factors for diabetes complications on the basis of individual characteristics. A full discussion of personalized approaches to nonglycemic risk factors is beyond the scope of this review, but diabetic nephropathy will be briefly discussed as an illustrative example.

Diabetes is one of the principal causes of chronic kidney disease, together with age, hypertension, and increased body mass index (44). Glycemic control...
strongly influences the development of diabetic nephropathy (45), and intensive blood glucose management strategies together with aggressive therapy of hypertension and dyslipidemia have contributed to a substantial reduction in the incidence of diabetic nephropathy (46, 47). Despite good control of glycemia and other risk factors, some patients still develop microalbuminuria and progressive renal dysfunction (48, 49). This is thought to result from additional genetic and environmental risk factors in individual diabetes patients. Familial clustering of nephropathy has been demonstrated in several studies (50–52), suggesting the presence of genetic factors that still are largely undefined. With candidate gene and genome-wide association approaches, genetic polymorphisms significantly associated with the development of nephropathy in type 1 and type 2 diabetes are now being defined, which have the potential to guide personalized decisions on therapy (53).

As an example, a polymorphism consisting of the presence or absence of an approximately 250-nucleotide sequence has been identified in the angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (ACE) gene (54). Although the polymorphic sequence is in a noncoding, intronic region of the gene, it appears to influence ACE gene expression. Individuals homozygous for the insertion (the II genotype) have lower levels of the ACE protein; individuals homozygous for the deletion (the DD genotype) have lower ACE concentrations, and I/D heterozygotes have intermediate values. Multiple studies support association of the II ACE genotype with a lower incidence of diabetic nephropathy and the I/D or DD genotypes with a higher incidence of nephropathy independent of glycemic control (55). The II genotype also is associated with a better antiproteinuric response to ACE inhibitor therapy compared with the I/D or DD genotypes (55). Although ACE inhibitors appear to have overall benefit in patients with advanced diabetic nephropathy independent of genotype and should be part of standard therapy, available data suggest that individuals with the II genotype may derive greater benefit from ACE inhibitor therapy in the early stages of nephropathy.

As a potential factor in more advanced nephropathy, genetic variants of the protein kinase C-β1 (PRKCB1) gene recently were found to associate with end-stage renal disease in type 2 diabetes (56). Further studies in additional populations are needed, but this raises the possibility that PRKCB1 genotyping might be useful in identifying individual patients who would benefit from intensive overall efforts at reducing diabetic nephropathy risk (e.g., intensive control of glycemia, blood pressure, and dyslipidemia) or might be particularly responsive to protein kinase C inhibitors that are under development. It can be anticipated that knowledge of these and additional genetic determinants of diabetic nephropathy risk, coupled with findings from proteomic and metabolomic analyses, will ultimately have a role in personalized decisions on how early to intervene and which agents to use in the prevention and management of diabetic nephropathy.

**Summary**

Diabetes mellitus is clearly established as a multifactorial disease with substantial heterogeneity within the broad subtypes of type 1 and type 2 diabetes. The recognition of this heterogeneity brings with it an a priori acknowledgement of the potential for individualized therapy. Driven by the recent advances in genetic and other molecular technologies, there is a strong interest in more personalized approaches to diabetes management. The success of this endeavor will require both new knowledge-based hypotheses for individualizing therapy and also strategies for testing these hypotheses. There is a need in particular for approaches to new drug development that include comparison in clinical trials of recognized diabetes subtypes as defined by clinical characteristics and molecular markers. This would require changes in the structure of drug trials, many of which are designed to be maximally inclusive of potentially heterogeneous patient groups to demonstrate drug efficacy in the broadest possible patient population.

The emphasis of this review has been on current and emerging knowledge of molecular markers that define individual disease subtypes on the basis of pathophysiology or response to specific therapies. It is important to appreciate that these types of molecular markers of disease individuality ultimately may influence decisions that range from specific drug choices to behavioral modification strategies. As an illustrative example not specifically related to diabetes, individuals homozygous for both the Y402H variant of the complement factor H (CFH) gene and the A69S variant of the age-related maculopathy susceptibility 2 (ARMS2) (LOC387715) gene have a 50-fold increased risk of adult macular degeneration (57). Cigarette smoking clearly multiplies this risk, and individuals with the Y402H/A69S genotype thus should be specifically targeted for behavioral modification as well as pharmacologic interventions to assist in smoking cessation.

At the same time that advancing knowledge of genetic, proteomic, and metabolomic characteristics of individuals with diabetes has given promise of more personalized approaches to diabetes management, it has brought concerns about limitations in this technology. Genome-wide association analysis depends on large numbers of patients to demonstrate statistically significant risk effects. This methodology has value in...
identifying genetic factors with influence in multiple populations and, thus, genetic factors with broad application in diabetes pathophysiology and treatment. However, it is important to recognize that genome-wide scanning is not structured to identify traits that may have effects of equal or even greater magnitude, but only on the genetic or environmental background of a specific population. The actual increase in risk associated with specific type 2 diabetes-associated markers identified by genome-wide scanning is on the order of 1.3- to 1.5-fold, and, in aggregate, all of the factors identified to date are estimated to account for no more than 10% of disease risk. This has led to concern that these advances in genetic knowledge may not provide enough information to direct diabetes management. These advances in genetic knowledge may not provide enough information to direct diabetes management until there is a complete understanding of disease mechanism (58). The application of systems biology methods to complex diseases such as diabetes mellitus is now being explored as a strategy for amplifying insights into pathophysiology and disease management by integrating the expanding amount of molecular data (59, 60).

Although much more research is needed, the strong evidence base for directed therapeutic strategies in the majority of patients with MODY, including discontinuation of glycemic therapies in MODY 2 and specific evaluation of response to sulfonylureas in MODY 1 and 3, provides a clear example of a beneficial application of molecularly driven personalized medicine in diabetes. While the data support a preferred therapeutic consideration, not all MODY 2 patients can be taken off therapy and not all MODY 1 and 3 patients can be managed effectively with sulfonylureas. It is likely that personalized medicine in more common forms of diabetes can have substantial benefit by similarly using individual patient characteristics to define a preferred sequence of options in treatment rather than one specific therapy.

References

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